ICU
MANAGEMENT & PRACTICE

2023
VOLUME 23
ISSUE 2

Organ Support

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Detecting Euglycaemic Diabetic Ketoacidosis Associated With SGLT2 Inhibitors

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SGLT2 inhibitor associated EDKA is becoming more prevalent due to the increasing use of SGLT2 inhibitors in cardiovascular medicine and type 2 diabetes. Physician awareness and knowledge about the disease and diagnostic tools need to improve for better management. Point of care blood testing for ketones can allow for rapid and accurate diagnosis.

Introduction

Euglycaemic diabetic ketoacidosis (EDKA) is an uncommon but potentially life-threatening emergency condition that is characterised by euglycaemia and elevated ketones in the presence of metabolic acidosis (Long et al. 2021; Lipscombe et al. 2018). Classically, diabetic ketoacidosis (DKA) is characterised by hyperglycaemia, an anion gap metabolic acidosis, and ketosis. DKA occurs typically in patients with type 1 diabetes and less frequently in patients with type 2 diabetes (Kitabachi et al. 2009). Munro et al. (1973) first recognised that diabetic ketoacidosis can be masked by euglycaemia. EDKA is defined by relative euglycaemia (serum glucose less than 13.9 mmol/l), bicarbonate less than 15 mmol/l, an anion gap greater than 12 mmol/l, and ketosis, leading to a pH in venous blood of less than 7.3 (Bonora et al. 2020; Rawla et al. 2017). Historically, 3 to 7% of the patients admitted to the hospital with diabetic ketoacidosis exhibited euglycaemia (Liu et al. 2020; Long et al. 2021).

More recently, EDKA has been associated with the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors (Diaz-Ramos et al. 2019; Liu et al. 2020; Rauch and Landmesser 2021), and the incidence of EDKA has risen because of increased use of these medications in patients with type 2 diabetes (Blau et al. 2021; Rawla et al. 2017). Patients with insulin-dependent diabetes are more prone to develop EDKA when treated with SGLT2 inhibitors (Blau et al. 2021; Rawla et al. 2017). Although the prevalence of SGLT2 inhibitor associated EDKA is on the rise, it is still relatively uncommon (approximately 2 per 1000 patients). SGLT2 inhibitor associated diabetic ketoacidosis may still be associated with significantly increased glucose levels, or more commonly, normal to slightly elevated glucose levels (Arzneimittelkommission der deutschen Ärzteschaft 2018). EDKA is often undiagnosed due to relatively low serum glucose levels, contributing to delayed therapy and worse clinical outcomes (Long et al. 2021; Blau et al. 2021).

Due to the overall increase in incidence of EDKA with more frequent SGLT2 inhibitor use, the United States Food and Drug Administration (FDA) and the European Medicine Agency (EMA) recently announced warnings, reminding prescribers and medical staff to be alert for SGTL2 inhibitor associated EDKA. Guidelines to reduce the occurrence of SGTL2 inhibitor associated EDKA have been added, especially to lessen the risk of developing ketoacidosis after surgery.

Pathophysiology of SGLT2 Inhibitor Associated EDKA

Absolute or relative insulin deficiency associated with insulin resistance contributes to the pathophysiology of EDKA (Kitabachi et al. 2009; Long et al. 2021; Modi et al. 2017). Elevated glucagon generation and release of free fatty acids triggers ketogenesis with production of ketone bodies, leading to acidosis (**Figure 1**). The synthesis of glucose is at least temporarily reduced due to fasting conditions, as is common under different triggers of stress, or, alternatively, the urinary glucose excretion is increased, e.g. as result of SGLT2 inhibitor intake (Bonora et al. 2020; Long et al. 2021; Rosenstock et al. 2015; Taylor et al. 2015). **Table 1** summarises the different conditions that can be associated with EDKA.

SGLT2 inhibitors were initially designed as antidiabetic drugs, which inhibit the sodium-glucose cotransporter 2 protein located in the proximal renal tubules (Rauch and Landmesser 2021). The inhibition of SGLT2 in the kidney abolishes the reabsorption of glucose from urine, contributing to increased insulin-independent excretion of glucose and sodium via the urine. In addition to reducing glucose levels SGLT2 inhibitors also decrease HbA1c values, blood pressure and weight. Importantly, several large randomised clinical studies have shown that SGLT2 inhibitors have cardioprotective and nephroprotective effects (The Nuffield Department of Population Health Renal Studies Group and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium 2022; Vaduganathan et al. 2022). SGLT2 inhibi-

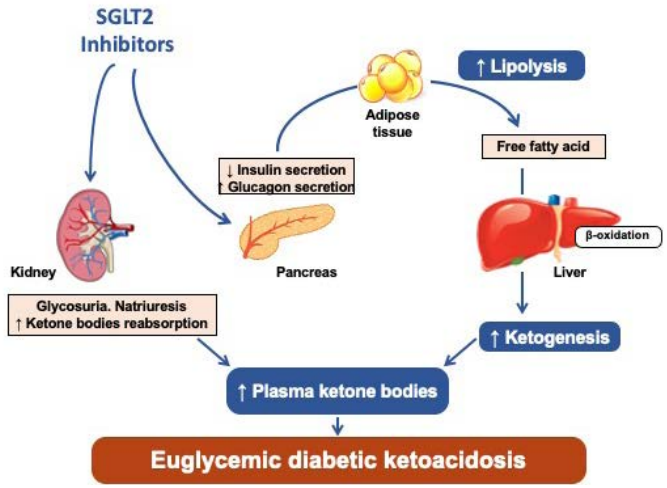

Figure 1. Effect of SGLT2 inhibitors on glucose and lipid metabolism

tors are indicated for the treatment of diabetes, heart failure and chronic kidney disease. The approved SGLT2 inhibitors in Germany include dapagliflozine, empagliflozine, ertugliflozine and sotagliflozine. Ipragliflozine, remogliflozine, sergliflozine and tofogliflozine are other SGLT2 inhibitors not approved in Germany. Due to the low benefit assessment, canagliflozin ceased to be sold in Germany in 2014. In Switzerland, canagliflozin, dapagliflozin and empagliflozin have been approved for use.

Due to the SGLT2 inhibitor associated increase in urinary glucose excretion and accompanied reduction in insulin secretion, serum glucose levels can be much lower in SGLT2 associated DKA than in other cases of DKA. In addition, SGLT2 inhibitors cause an increased reabsorption of ketone bodies in the kidney and, therefore, increase ketone levels in the circulating blood. The heightened level of ketones triggers ketoacidosis, measurable as anion gap (Bonner et al. 2015; Ferranini et al. 2014; Pfützner et al. 2017).

In several studies, it was noted that 12% to 20% of patients with type 2 diabetes that were treated with SGLT2 inhibitors had an asymptomatic elevation of ketone bodies in blood (Modi et al. 2017; Rawla et al. 2017). Moreover, the majority of SGLT2 inhibitor associated diabetic ketoacidosis was found to be EDKA with a glucose level below 13.9 mmol/l. Regarding the increased risk of EDKA a hazard ratio (HR) of 3.58 was reported for canagliflozin, a HR of 2.52 for empagliflozin and of 1.86 for dapagliflozin (Douros et al. 2020). Of note, the likelihood to suffer from EDKA is greater in patients on SGLT2 inhibitors who have decreased glycogen stores or a lower body mass index (Handelsman et al. 2016).

- SGLT2 inhibitor use
- Fasting state, perioperative setting
- Surgery, e.g. bariatric operations
- Ketogenic diet
- Anorexia
- Intoxication, alcohol, cocaine
- Insulin pump
- Gastroparesis
- Glycogen storage disease
- Infections, sepsis
- Gastroenteritis, pancreatitis
- Renal disease
- Liver disease
- Pregnancy

Table 1. Conditions for increased risk of EDKA

Diagnostic Tools for the Assessment of SGLT2 Inhibitor Associated EDKA

The clinical signs and symptoms of patients with EDKA are comparable to those with diabetic ketoacidosis with elevated blood glucose levels (Long et al. 2021; Modi et al. 2017). Unfortunately, most of these symptoms are vague and non-specific (e.g., nausea, exhaustion, abdominal pain, confusion, kissing mouth breathing (Long et al. 2021; Modi et al. 2017). Several clinical courses have been described with SGLT2 inhibitor associated EDKA, leading to life-threatening conditions. Thus, a high index of suspicion for EDKA should be maintained in this patient group, and checking ketones with a point of care device can establish the diagnosis and be lifesaving. Roughly half of the patients with EDKA have a delay in diagnosis (Dizon et al. 2017). Moreover, these patients often come late to the emergency room because home measurements of blood glucose are not significantly increased (Modi et al. 2017). A fruity odour of the breath is a characteristic feature of ketoacidosis together with dehydration visible as dry skin with reduced skin turgor, a dry tongue and mucous membranes. Usually, the patients exhibit tachycardia accompanied with hypotension, the shock index is often positive and admission to intensive care treatment immediately required. To prevent the delay of diagnosis, EDKA should not only be considered in any diabetic patient on SGLT2 inhibitor therapy but also in those with risk factors for EDKA, such as alcohol intoxication, chronic liver disease, fasting conditions, or typical clinical presentation of symptoms as mentioned above (Dhatariya 2016). Early ketone measurement can quickly establish or rule out the diagnosis.

Electrolytes, glucose, creatinine and eGFR as well as liver enzymes, venous blood gas, and serum ketones comprise the laboratory evaluations, which should be performed in case of suspected EDKA. Due to above mentioned euglycaemia in EDKA, elevated glucose levels in blood are not a good indicator of SGLT2 inhibitor associated DKA. A pH of less than 7.30, bicarbonate less than 14 mmol/l and elevated anion gap more than 12 mmol/l as well as ketone bodies are typical for diabetic ketoacidosis. Blood ketones (specifically β-hydroxybutyrate) are the predominant ketone bodies in DKA and have a higher sensitivity and specificity for DKA than urine ketones. In contrast to blood ketones, urine ketone levels in patients treated with SGLT2 therapy might be falsely low due to reabsorption of ketone bodies from the

Category	Blood ketones	Urine ketones
Parameter (measured)	β-hydroxybutyrate as ketone body predominantly produced in DKA measures current concentration, progress controls useful for therapy monitoring	Acetoacetate as by-product measures average urine concentration
Reliability of results	Higher sensitivity and specificity for DKA	Lower sensitivity and specificity for DKA
Time	Rapid, immediate measurement	Possibly delayed at sample collection due to dehydration
Measurement method	POCT meter	Urine test (strip)

Table 2. Comparison of the advantages and disadvantages of ketone measurement methods
DKA = diabetic ketoacidosis. Adapted according to Dhatariya et al. 2016

urine in the tubules of the kidney, leading to a false negative result (Handelsman et al. 2016; Long et al. 2021).

Guidelines recommend using β- hydroxybutyrate in blood as the diagnostic test in the assessment of EDKA (Handelsman et al. 2016). Assessing β-hydroxybutyrate is preferable rather than relying on acetoacetate, because of the much higher concentration of the β-hydroxybutyrate than acetoacetate in blood (ratio of 7-10:1) (Dhatariya 2016; Handelsman et al. 2016; Long et al. 2021; Kilpatrick et al. 2022). Serum β-beta-hydroxybutyrate levels > 3 mmol/L in paediatric patients and > 3.8 mmol/L in adults are reliable for diagnosing DKA (Arora et al. 2011; Kilpatrick et al. 2022; Sheikh-Ali et al. 2008). If serum beta-hydroxybutyrate is not available, serum acetoacetate and/or urine ketones can be utilised, although these measurements are less specific and sensitive for EDKA.

Blood ketone measurements offer other advantages as well. Blood is easily obtained, where urine may not be due to the dehydration associated with DKA (Kilpatrick et al. 2022; Dhatariya 2016). By using a point-of-care method directly at the site of the patients, measurements can be carried out immediately and results are obtainable within seconds. Thus, the assessment of blood ketone levels by a point-of-care system is today the fastest and most practical method to guarantee a fast and reliable diagnosis (**Table 2**). Although some disparity regarding the use of blood ketones to assess the success of treatment exists, the contemporary identification and management of patients with suspected diabetic ketoacidosis makes even more use of the measurement of blood ketones than some guidelines currently recommend (Kilpatrick et al. 2022).

Conclusion

SGLT2 inhibitor associated EDKA is becoming more prevalent due to the increasing use of SGLT2 inhibitors in cardiovascular medicine and type 2 diabetes. EDKA is often misdiagnosed or diagnosed late due to relatively low serum glucose, contributing to delayed therapy and worse clinical outcomes. The physician's awareness and knowledge about the disease and diagnostic tools need to improve for better management of patients with EDKA. Point of care blood testing for ketones can allow for a rapid and accurate diagnosis.

Key Points

- Diabetic ketoacidosis is a serious metabolic derailment of diabetes caused by insulin deficiency and is usually characterised by hyperglycaemia as well as ketosis and acidosis.
- Euglycaemic diabetic ketoacidosis (EDKA) has become a major topic of discussion due to its increased incidence associated with the widespread use of SGLT2 inhibitors.
- SGLT2 inhibitors increase renal glucose excretion, reduce blood glucose level and increase the formation and accumulation of ketone bodies, which is further augmented by an increased absorption of ketone bodies in the kidney.
- SGLT2 inhibitor associated EDKA is often undiagnosed or diagnosed late due to relatively low serum glucose levels.
- The diagnosis of EDKA should be suspected in patients on SGLT2 inhibitors and ketones should be measured promptly to avoid progression to life-threatening disease.
- Guidelines recommend measuring the pH together with ketones in blood but not urine as the most specific and sensitive method.
- Serum ketones can easily be quantified by point-of-care systems, which is a fast and practicable method to ensure the diagnosis of EDKA.

Disclaimer

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